Applicant : **Henry Lardy, et al.**
Application No. : **09/675,323**
Filed : **September 28, 2000**
Title : **Therapeutic Treatment of Androgen Driven Conditions**
Examiner : **Elli Peselev**
TC/A.U. : **1623**

Docket No. : **HOLISED.063A**
Customer No. : **26551**
Confirmation No. : **2363**

DECLARATION UNDER 37 CFR § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

We, Henry A. Lardy and Padma Marwah declare as follows:

1. We are the inventors of the above-referenced patent application. The following statements are based on the documents identified below, our personal knowledge of the facts and results that are discussed below.

2. We are coauthors of the H-C. Chang, et al., publication (*Proc. Natl. Acad. Sci USA*, 96:11173-11177, 1999). We were aware of the contents of this reference before it was submitted for publication. I, Henry A. Lardy, contributed the Chang et al. reference for publication as shown at the attribution statement: "*Contributed by Henry Lardy, August 5, 1999*" on page 11173. The information in this publication was therefore necessarily in my possession before the article published. The manuscript that the journal received for publication on August 5, 1999 was thus a written reduction to practice for all of the information in the article that existed on that date, which predates the article's publication on

September 28, 1999. Exhibit 1 is information the journal has provided showing that the first date the article was mailed to subscribers was September 28, 1999.

3. We selected the compounds that were described in Chang, et al. to inhibit the capacity of androst-5-ene-3β,17β-diol (referred to as 'Adiol' in Chang, et al.) to activate androgen receptor transcriptional activity. We alone selected the compounds on the basis of structural activity relationships, a full description of which has been subsequently published (Marwah, P., et al. *Bioorg. Med. Chem.*, 14:5933-5947, 2006, newly cited).

4. I, Henry A. Lardy, had all of the compounds, which are described in Chang, synthesized in my laboratory or commercially purchased under my direction. The attached sheet at Exhibit 2 is from a laboratory notebook describing the melting point for compound 10 (androst-5-ene-3β-methylcarbonate-7,17-dione). This information was in my possession before I, Henry A. Lardy, submitted the Chang, et al. reference to the journal for publication. The assay described in the Chang, et al. reference was essentially the same assay that was published earlier (H. Miyamoto et al., *Proc. Natl. Acad. Sci. USA*, 95:11083-11088, 1998, of record) showing that androst-5-ene-3β,17β-diol could activate androgen receptor transcriptional activity. I, Henry A. Lardy was a coauthor of the Miyamoto et al. publication, and I was thus familiar with the assay and protocols it described before I contributed the Miyamoto et al. reference for publication as shown by the attribution statement: "*Contributed by Henry Lardy, July 29, 1998*" on page 11083.

5. I, Henry A. Lardy, sent the compounds, including compound 10 that were described in Chang et al. to Dr. Chang's laboratory for characterization of their activity using the previously published Miyamoto, et al. assay and the assay described in the Chang, et al. publication. The compounds were sent with the molecular weights for each. Detailed structures were sent only after they had

sent us the results of the assays. The attached sheet at Exhibit 3 is from a laboratory notebook showing that compounds, including Compound 10, were sent to Dr. Chang's laboratory coded, and only we knew the results and chemical structures for individual compounds in the assay before any personnel in Dr. Chang's laboratory was aware of this. In view of the facts, none of the subject matter that is now disclosed or claimed in this patent application and disclosed in Chang, et al. was or could have been invented by or derived from any of the other Chang, et al. authors.

6. We hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 21, 2007 By: /Henry A. Lardy/
Henry A. Lardy

Date: February 21, 2007 By: /Padma Marwah/
Padma Marwah

Exhibit 1
(2 sheets attached)

◂ Previous Article | Table of Contents | Next Article ▸

Vol. 96, Issue 20, 11173-11177, September 28, 1999

Biochemistry

Suppression of Δ^5-androstenediol-induced androgen receptor transactivation by selective steroids in human prostate cancer cells

Hong-Chiang Chang*, Hiroshi Miyamoto*, Padma Marwah†, Henry Lardy†, Shuyuan Yeh*, Ko-En Huang*, and Chawnshang Chang*,†,‡

* George Whipple Laboratory for Cancer Research, Departments of Pathology, Urology, Radiation Oncology, and the Cancer Center, University of Rochester Medical Center, Rochester, NY 14642; and † Institute for Enzyme Research and Comprehensive Cancer Center, University of Wisconsin, Madison, WI 53705

Contributed by Henry Lardy, August 5, 1999

Our earlier report suggested that androst-5-ene-3β,7β-diol (Δ^5-androstenediol or Adiol) is a natural hormone with androgenic activity and that two potent antiandrogens, hydroxyflutamide (Eulexin) and bicalutamide (Casodex), fail to block completely the Adiol-induced androgen receptor (AR) transactivation in prostate cancer cells. Here, we report the development of a reporter assay to screen several selective steroids with anti-Adiol activity. Among 22 derivatives/metabolites of dehydroepiandrosterone, we found 4 steroids [no. 4, 1,3,5 (10)-estratriene-17α-ethynyl-3,17β-diol; no. 6, 17α-ethynyl-androstene-diol; no. 8, 3β,17β-dihydroxy-

This Article

- Full Text
- Full Text (PDF)
- Alert me when this article is cited
- Alert me if a correction is posted
- Citation Map

Services

- Similar articles in this journal
- Similar articles in ISI Web of Science
- Similar articles in PubMed
- Alert me to new issues of the journal
- Add to My File Cabinet
- Download to citation manager
- Cited by other online articles
- Search for citing articles in: ISI Web of Science (22)
- Request Copyright Permission

Google Scholar

- Articles by Chang, H.-C.
- Articles by Chang, C.
- Articles citing this Article

PubMed

- PubMed Citation
- Articles by Chang, H.-C.
- Articles by Chang, C.
- Pubmed/NCBI databases
  - Compound via MeSH
  - Substance via MeSH

Medline Plus Health Information
- Prostate Cancer

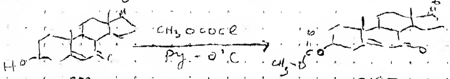
androst-5-ene-16-one; and no. 10, 3β-methylcarbonate-androst-5-ene-7,17-dione] that have no androgenic activity and could also block the Adiol-induced AR transactivation in prostate cancer PC-3 cells. Interestingly, these compounds, in combination with hydroxyflutamide, further suppressed the Adiol-induced AR transactivation. Reporter assays further showed that these four anti-Adiol steroids have relatively lower glucocorticoid, progesterone, and estrogenic activity. Together, these data suggest some selective steroids might have anti-Adiol activity, which may have potential clinical application in the battle against the androgen-dependent prostate cancer growth.

‡ To whom reprint requests should be addressed. E-mail: chang@pathology.rochester.edu .

 0027-8424/99/9611173-5$2.00/0

Exhibit 2
(1 sheet attached)

[redacted]



302 → 360

7oxo DHEA = 0.5 g (0.00165 mol)
Py = 5 ml

Me-chloroformate = 0.19 gm = (0.002 mol)
(94.5)
Py — 6 ml

Soln of 7oxo DHEA was taken in Py cooled to 0–5°C & to it slowly Me-chloroformate at 0°C dropwise temp is to be maintained at 0–5°C throughout stir at 0°C for another 2–3 hrs. ~90% reaction over. poured into water & extd with DCM - wash dry & chromatographed product eluted with 20% Acetone-hex. gave white solid - cryst from aq. MeOH (2:8) = 0.42 gms
SM → 1 gms

89% Based on 80% conversion

mp - 168-70°C

Exhibit 3
(1 sheet attached)

[redacted]

Compounds sent to Chaurnsheng C

androstene diol -16-one —

4-estren-17α ethynyl-3B,17B diol —

4-estren-17α " -17B-ol-3 one. +
4-androstene-17α " 17B-ol-3-one +
Δ5-Androstenol 17α " 3B,17B-diol —

1,3,5(10) Estratriene 17α-ethynyl-3, 17B-diol —
This is a [illegible] contraceptive

Previously sent:

7-oxo-diol (#22) and 19-nor-diol #23

[redacted] Compounds sent to Dr. Chang

3B-methylcarbonate of 7-oxo-DHEA —
3B-acetoxy androstene-17B TB di Me Silyl ether -7-one
3B-methoxy androst-5-ene-7B,17B-diol —

3B-Methoxy-17B-hydroxyandrost-5-en-7-one —

17-methyl ester of marianolic acid ? —

[redacted]

3B,17B-dihydroxyandrost-5-en-16-one
3B,17B-dihydroxyandrost-5-en-11 one — 8
3B,11B,17B-trihydroxyandrost-5-ene — 1
? 3B-acetoxy-7α,17B dihydroxyandrost-5-ene — 1
3B,17B-diol androst-4-ene.
? 5(10)Estren-17α-ethynyl-17B-ol-3-one + 2
3B,17B-diacetoxyandrost-5-en-7-one
17B-Hydroxyandrost-3,5-diene-7 + 1